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(54) Cement for medical use, method for producing the cement, and use of the cement.

(57) In a method for producing a cement for medical use, a liquid component containing a polymerizable substance is combined with a solid component comprising a plastic substance to provide a setting mass to form the cement. In order to e.g. improve the biological and mechanical properties of the cement and allow it to be mixed by modern mixing procedures, which further improves the cement quality, said plastic substance is mixed with a particulate crystalline ceramic material prior to combining said liquid and solid components. A cement for medical use is also defined as is the use of set cement as an anchorage for the fixation of prostheses or parts of prostheses or bone and as a substitute material for bone.

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This invention relates to a method for producing a cement for medical use according to which a liquid component containing a polymerizable substance is combined with a solid component comprising a plastic substance to provide a setting mass to form the cement. The invention also relates to a cement for such uses and to the use of set cement as an anchorage for the fixation of prostheses or parts of prostheses or bone and as a substitute material for bone.

The use of anchorage substances in surgical procedures, especially for implants, has led to the development of so-called bone cement. The most common use of bone cement has been to fill the gap between a joint implant and tissue, primarily bone. As the cement sets around an implant immediate fixation will be achieved. This is especially important in the often severly handicapped elderly group of patients being operated with joint implants. When bone cement is used weight bearing is generally allowed within the first postoperative days. The most important complication hitherto has been infection, joint implants breakage or dislocation. Through strict aseptic and antiseptic measures and methodologic development the most severe problems today are wear of the polymer component and loosening between the metallic and polymer implants and bone leading to an interface failure with bone resorption and loss of implant anchorage. An improvement of material and technique has been going on since joint implant procedure with the bone cement started in the late 1950's through cooperation between researchers, engineers, manufacturers and surgeons.

The most important development in the area of bone cement has been a change of the additives used in bone cement. Various substances with particles between 20-300 micrometers in size have been used. Particulate additive powder has mainly been used in a spherical form. This may be regarded as the accepted technique today. Both resorbable particulate powder such as tri-calcium phosphate and non-resorbable powder such as zirconium oxide have been used. The addition of particulate powder varies between 5-30% with 20-25% regarded as optimum. In contrast to the additives which have a secondary role, for example zirconium oxide or barium sulphate which give a radiopaque bone cement, and tri-calcium phosphate which gives a porous cement, new additives will have to be developed to improve both the biological and mechanical properties of bone cement.

The aim of this invention has been to develop additives which improve the mechanical properties of bone cement and the tissue interface reaction giving a quicker bone or tissue in-/ongrowth to the implant.

A further aim has been to reduce the radioactivity from zirconium oxide but still allow the bone cement to be mixed by modern mixing procedures, which further improves cement quality and reduces monomer exposure in the operating area. Adding crystalline ceramic particulate powder to the polymer methacrylate will resolve some of the problems given above. It is important that a ceramic additive is produced in the classic way in the temperature curve span where the sintering of particulate powder takes place. It excludes dried powder or powder produced through agglumeration. Ceramic powder for bone cement may be produced in two different ways. The first possibility is to produce a synthetic or biological powder with the requested homogeneity followed by sintering in an oven. The sintered beads will then be ground, a procedure that is technically known. After selection of the distribution and size of beads the crystalline ceramic powder is added to the bone cement. The second possibility is to use the above described powder together with water or other solutions in order to get a dough with a microporosity through a special working procedure which dough then will be sent for drying. The mixture will be sintered in the classic way. In the following descripton of the invention the first method is used.

To improve the interface and the biological tissue ingrowth it is according to the invention important that the size of the beads is smaller than those previously used.

At least 50% of the added beads should be less than 50 micrometers with a gaussian curve of distribution and at least 50% of the above additive should be less than 3 micrometers. By using this bead size and distribution the rheological properties of the invented bone cement will be enhanced and the contact area increased at the cement surface. This allows for a rapid tissue ingrowth. It is possible to add further separate crystalline ceramic additives according to the procedure above.

Antibiotics containing bone cement have been used since the beginning of the 70's. The antibiotic granulate is dissolved from the surface of the bone cement. This gives a high antibiotic tissue concentration thereby killing bacteria pre- and postoperatively. The antibiotics may be administered in the bone cement in three different ways. The first way is to add powder to the cement. The second way is to add antibiotics to the seperate crystalline ceramic beads through a pharmaceutical procedure as for instance after soaking in an antibiotic solution. The antibiotics will then be administered into bone cement together with crystalline powder. By this procedure the antibiotics will be at the surface of the additive. This gives the advantage of administering antibiotics with extremely variable acting

mechanisms. It is also possible to use a combination of antibiotics both in the bone cement as a powder as well as by integration into the additive ceramic crystalline powder.

The third possibility is to add antibiotics as a solution to the bone cement.

Finally, to avoid absorption of monomer fluid to a considerable extent by the porous particles, the pores can be filled with monomerisable material with a low consistency. After polymerization it might be necessary to grind the material in order to achieve the desired particle size.

The possibility of using cement application in humans today depends on whether or not it could be used in delivery systems, especially in combination with vacuum. This could be achieved by using an appropriate viscosity (rheological properties) of the bone cement. The bone cement defined above will preferably be used together with vacuum and injected into humans through a delivery system with a cement viscosity that allows this procedure.

By using the bone cement according to the invention in a closed system during mixture and delivery no transfer of the bone cement is necessary. One such suitable system is so-called Preepack in which the solid and liquid components are contained separated from each other in different individual chambers within one and the same container, wherein the chambers are connected to each other when the components are to be combined.

By adding heat to the bone cement during the mixing procedure the setting time will be reduced; and by chilling the bone cement the setting time will be increased. By using different temperature intervals it will be possible to individualize the setting time of the above described bone cement according to the invention.

The main area of the above described bone cement is to be used in anchoring joint implants or bone and as a bone substitute.

Example 1

A synthetically produced hydroxyl apatite powder is mixed with a synthetic zirconium oxide in a proportion of 8:2. The powder is heated to 1250 °C with a soft powder shaking procedure. This is followed by a grinding procedure and classification of the powder. As an example 5g of the crystalline ceramic beads thus produced will be added to 35g of bone cement to achieve polymerization and the monomer will be filled separately.

Example 2

As example 1 with the exception that zirconium oxide is replaced with aluminium oxide.

Example 3

As in example 1 in which a non-ionic crystalline X-ray contrast aid preferably lohexol is used instead of zirconium oxide.

Example 4

As in example 1 in which crystalline ceramic calcium phosphate is used instead of zirconium oxide.

Example 5

As in example 1-4 with the exception that a metallic ceramic powder is used.

Example 6

As example 1-5 with an antibiotic powder added.

Example 7

As example 1-6 where the monomer is mixed with an addition of antibiotics.

Example 8

As in example 1-4 with crystalline ceramic powder which is soaked and dried with antibiotics prior to the mixing.

Example 9

10g of crystalline particles are soaked with methyl methacrylate containing a polymerization starting system. After curing for 24 hours the material is ground, classified and added to the bone cement powder in order to get 5g of crystalline ceramic in 45g of polymer powder.

Claims

1. Method for producing a cement for medical use, in which a liquid component comprising a polymerizable substance is combined with a solid component comprising a plastic substance to provide a setting mass which is set to form the cement, **characterized** in that said plastic substance is mixed with a particulate crystalline ceramic material prior to combining said liquid and solid components.

2. Method according to claim 1, **characterized** in that said particulate crystalline ceramic material is chosen among calcium phosphate, zirconium oxide or non-ionic contrast aid, hydroxyl apatite, alumina, metallic ceramics and combinations thereof.

3. Method according to claim 1 or 2, **characterized** in that said particulate crystalline ceramic material is a mixture of calcium phosphate/alumina or calcium phosphate/zirconium oxide.

4. Method according to any of claims 1-3, **characterized** in that crystalline ceramic calcium phosphate is mixed with a non-ionic X-ray contrast aid, preferably lohexol.

5. Method according to claim 4, **characterized** in that at least 50% of the particulate material has a particle size of less than 20 microns.

6. Method according to claim 4, **characterized** in that the particle size distribution of said particulate material follows in general a gaussian curve of distribution.

7. Method according to claim 5 or 6, **characterized** in that at least 50% of the gaussian distributed particles have a particle size of less than 3 microns.

8. Method according to claim 1 and 3, **characterized** in that the particulate sintered crystalline ceramic material is mixed with the solution, preferably acrylate, the setting mass is grinded to a particle size wherein at least 50% of the particulate material has a particle size of less than 20 microns, and/or wherein the particle size distribution of said particulate material follows in general a gaussian curve of distribution and/or wherein at least 50% of the gaussian distributed particles have a particle size of less than 3 microns.

9. Method according to any of the preceding claims, **characterized** in that an antibiotic or a mixture of antibiotics is contained in either of said solid or liquid components.

10. Method according to any of the preceding claims, **characterized** in that the mixing of said solid and liquid components as well as the application of the setting mass are carried out under vacuum.

11. Method according to any of the preceding claims, **characterized** in that said solid and liquid components are contained or packed in different individual chambers of a common container (so-called Preepack).

12. Method according to claim 11, **characterized** in that a communication is provided between said individual chambers so as to bring about the mixing of said solid and liquid components within the common container.

13. Method according to any of the preceding claims, **characterized** in that the setting characteristic of the setting mass is adjusted through supply or withdrawal of heat.

14. Use of a cement as obtained through the method according to any of claims 1-13 as an anchoraging means to fix prostheses or parts of prostheses.

15. Use of a cement as obtained through the method according to any of claims 1-13 as a bone substitute.

16. Use of a cement as obtained through the method according to any of claims 1-13 as an anchoraging means to fix bone.

17. Cement for medical use, **characterized** in that it comprises one crystalline ceramic material.

18. Cement according to claim 17, **characterized** in that said crystalline ceramic material is selected from the group consisting of calcium phosphate, zirconium oxide, hydroxyl apatite, alumina, metallic ceramics, non-ionic contrast aid or combinations thereof.

19. Cement according to claim 17 or 18, **characterized** in that said material is an X-ray contrast aid, preferably lohexol.

20. Cement according to any of claims 17-19, **characterized** in that it also contains an antibiotic or a mixture of antibiotics.

21. Cement according to any of claims 17-20, **characterized** in that at least 50% of said material has a particle size of less than 20 microns.

22. Cement according to any of claims 17-20, **characterized** in that the particulate crystalline ceramic material has particle sizes distributed in accordance with a gaussian curve of distribution.

23. Cement according to claim 22, **characterized** in that at least 50% of said particulate material has a particle size of less than 3 microns.

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EUROPEAN SEARCH REPORT

Application Number
EP 94 11 2724

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 511 868 (ONODA CEMENT COMP.,LTD.) * examples *	1,2,5, 14-18,21	A61L25/00
X	GB-A-2 156 824 (MEISHINTORYO CO LTD.) * claims; examples *	1,2	
Y	DE-A-40 16 135 (TOKUYAMA SODA KK) * claims; examples *	1-23	
Y	FR-A-2 606 282 (ECOLE NATIONALE SUPERIEURE DE CERAMIQUE INDUSTRIELLE.) * examples *	1-23	
Y	EP-A-0 242 672 (MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG.) * claims; examples *	1-23	
A	DE-A-37 30 298 (SHOWA DENKO KK) * claims *	1-23	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	EP-A-0 301 759 (PFIZER HOSPITAL PRODUCTS GROUP, INC.) * column 1, line 30 - line 37; claims *	1	A61L
A	EP-A-0 190 504 (JOHNSON MATTHEY PUBLIC LTD. COMP.) * page 3, line 6 - line 26 * * page 4, line 1 - line 22 * * page 5, line 7 - line 14; claims *	1	
A	US-A-4 668 295 (PRAPHULLA K. BAJPAI) * examples *	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17 November 1994	ESPINOSA, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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T : theory or principle underlying the invention
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